Nothing tends so much to the advancement of knowledge as the application of a new instrument.
Sir Humphrey Davy

Why Not Use It All?

One of the prominent features of the recent Annual Meeting of the Society of Toxicology (SOT) in New Orleans, Louisiana, was the debate on a hypothetical motion to have the results of mechanistic toxicity studies supersede ambiguous epidemiological data in chemical risk assessments for humans. The audience was polled prior to the debate, but the results have little to say about the merits of the question. The motion itself is flawed, as either a vote for or against could well prevent the assumed underlying goal of strengthening the science base on which public health policy decisions are made. The motion implies that one should choose either weak epidemiology data or mechanistic information. However, both mechanistic data and epidemiological findings are often suggestive, but not conclusive, when taken alone. With this in mind, it seems imprudent to discard one set of inconclusive data for another set of inconclusive data.

Instead, scientists and policy makers should attempt to integrate all of the available data into health risk assessments. Integration of diverse data sets arising from human studies, animal toxicological studies, and mechanistic studies requires input from multiple scientific disciplines. Most importantly, it requires reliance on sound scientific judgment. Though difficult, this approach maximizes the use of all relevant information in public health decisions, and if properly organized and not overly prescriptive, can provide a template for describing uncertainty and research approaches that could reduce this uncertainty.

The timing of the SOT motion is somewhat puzzling, considering that many public health agencies and institutions are already moving away from sole reliance on single data sets or exclusive guidelines for decision making. The examples are numerous and include the U.S. Environmental Protection Agency (EPA), the International Agency for Research on Cancer (IARC), the U.S. Food and Drug Administration (FDA), and the National Toxicology Program (NTP). In the case of the EPA, the proposed revised guidelines for cancer and noncancer risk assessments explicitly require a "weight of evidence" approach in risk assessments (*1*).

Currently, the draft revised guidelines are being applied to risk assessments for dioxin, chloroform, butadiene, and others. Lessons learned from these applications will be instructive in improving the process by which the guidelines are applied. For example, the EPA's mandate to evaluate which risk assessment circumstances for children will require the use of additional uncertainty factors will benefit from new methods for integrating data from human, toxicology, and mechanistic studies by providing a more rational basis on which to decide whether to apply such factors and, if so, what the magnitude of such factors should be. Bill Farland, director of the EPA's National Center for Environmental Assessment, has been a strong advocate for implementation of the proposed revised guidelines. In contrast, exclusion of relevant data, because it is not conclusive by itself, would diminish the EPA's effort to make decisions on a scientific basis.

In 1992, IARC revised its guidelines for classification of carcinogens (*2*). The new guidelines, like the EPA's proposed risk assessment guidelines, call for the use of mechanistic data along with human epidemiological and animal cancer data by the working groups that determine whether an agent is a known, probable, or possible human carcinogen, or if the agent lacks carcinogenic activity or cannot be classified. These guidelines were used to upgrade ethylene oxide and dioxin to the "known human carcinogen" category and to downgrade the classification of saccharin. These classifications are not without controversy in that legitimate scientific debate remains, but they demonstrate that diverse data sets can be successfully integrated into an overall assessment or classification.

The NTP is mandated by Congress to prepare a report that lists agents to which a significant number of people in the United States are exposed as either known or reasonably anticipated to be human carcinogens. The NTP, like IARC, has revised the criteria for listing in the report to explicitly require consideration of all relevant data in the listing process (*3*). The new criteria, like IARC and EPA, specify the use of human data, animal data, and mechanistic data, and state that "conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment with consideration given to all relevant information." The new criteria are now being applied to determine listings of nearly 25 agents or substances in the ninth *Report on Carcinogens*, due to be published later this year. Listings being considered include environmental tobacco smoke, alcoholic beverages, crystalline silica, and benzidine-based dyes as "known human carcinogens"; methyl *tert*-butyl ether (MTBE) and diesel particulates as "reasonably anticipated to be human carcinogens"; and the delisting from the report of saccharin and ethyl acrylate. Delisting means that they are characterized as something less than "reasonably anticipated to be a human carcinogen." These delistings are based on proposals that the mechanism by which saccharin and ethyl acrylate cause cancer in animals would not operate in people exposed to those substances. Taken together, the efforts described above respond to the growing recognition that multidisciplinary approaches are needed to better link scientific knowledge to public health policy.

The SOT motion used chloroform and saccharin as examples of situations for which mechanistic data would be used to discount equivocal results from epidemiology studies. No one, of course, is recommending that strong epidemiological evidence should be discounted. But the SOT debate was unbalanced in that it did not address examples for which positive mechanistic data could be used to establish risk in the presence of weak or nonexisting epidemiological data. The use of mechanistic data, including molecular epidemiology studies and its interplay with evidence from traditional epidemiology studies, must function both to upgrade and downgrade the classification of substances. The EPA, IARC, NTP, and FDA are explicit in their statements that mechanistic data can be used to upgrade the results of inconclusive epidemiology data as well, as to downgrade. Examples for which such data were used to upgrade classification of a substance should have been included as part of the SOT debate.

Our growing understanding of the biological processes that cause human disease are creating difficult challenges and also unprecedented opportunities to link science to public health policy.

We need to develop ways to better strengthen this link instead of creating polarized views that only add to public confusion concerning regulatory decisions by asking people to make choices based on often-misleading extremes. It has been said that too much knowledge can be a dangerous thing. Too little can be, as well.

George W. Lucier
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References and Notes

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3. NTP. Report on Carcinogens. 8th ed. Research Triangle Park, NC:National Toxicology Program, 1998.